# Late stage C—H activation of a privileged scaffold; synthesis of a library of benzodiazepines

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# Late Stage C–H Activation of a Privileged Scaffold; Synthesis of a Library of Benzodiazepines

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This paper is dedicated to Professor Michel Pfeffer (ULP, Strasbourg) for his contributions to C–H activation and palladacycle chemistry.

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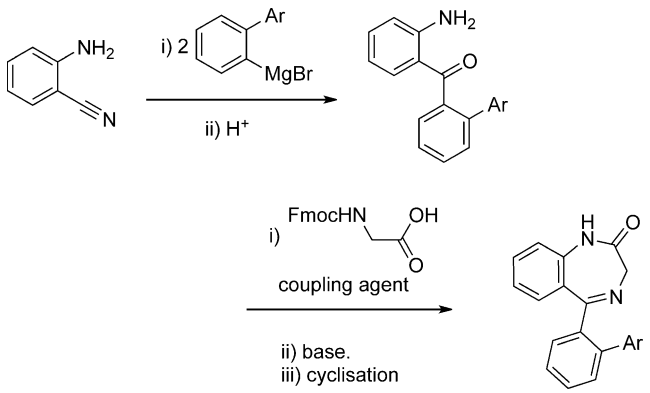
**Abstract:** A library of over twenty 5-(2-arylphenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones has been formed by a microwave-mediated late-stage palladium-catalysed arylation of 1,4-benzodiazepines using diaryliodonium salts. This can also be applied to nordazepam (7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one), the active metabolite of diazepam, and subsequent N-alkylation and/or H/D exchange allows further diversification towards elaborated pharmaceuticals and their 3,3′-deuterated analogues.

**Keywords:** C–H activation; deuteration; heterocycles; microwaves; palladium

## Introduction

The need for efficiency in rapidly producing a library of closely related analogues cannot be understated in drug discovery where natural product derivatives or complex molecules, often synthesised by multistep reactions, are fine-tuned to respond to inadequacies in terms of their biological activity, selectivity, pharmacokinetics and undesirable toxicity. The ability to add functionality to a bioactive core at the final or penultimate synthetic step to enable SAR (structure–activity relationship) studies can drive efficiency and speed up hit-to-lead and lead optimisation strategies.[1]

We have a longstanding interest in benzodiazepines, which represent an important class of privileged heterocycles.[2] Typical routes for the introduction of different R groups at the 5-position are inefficient since such reactions are early in the synthetic sequence and this is followed by repetitive coupling/cyclisation chemistries (Scheme 1).




**Scheme 1.** A classical route to a 5-(2-arylphenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

## Results and Discussion

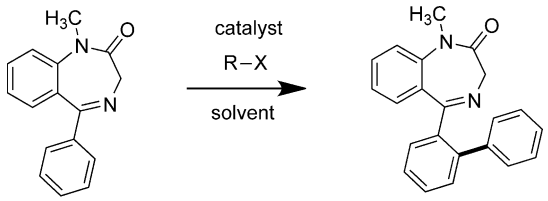
Our approach sought to vary the 5-substituent *via* a late-stage C–H activation; in essence, a benzodiazepine building block could be synthesised, once, on a large scale using the coupling/cyclisation chemistry discussed above, then functionalised by introducing the new functional groups at the last step, adding atom and step economy[3] to the library generation process. Our test case was the chelation-assisted C–H activation of the valium (diazepam)-like benzodiazepine **1a** using palladacycle chemistry to afford **2a** (Table 1).[4] Notably, Cintrat et al. showed that *ortho*-halogenation[4c] of the aryl group can be achieved under similar conditions, opening up the possibility of carrying out complementary Pd-mediated couplings. A rapid screen of conditions showed that this was indeed possible and that the best conversions, by $^1$H NMR, involved acetic acid as solvent, microwave conditions,[5] and employed 5 mol% $Pd(OAc)_2$ as catalyst and $Ph_2IBF_4$[6] as the arylating agent (entry 2). The use of a mesityl-aryliodonium salt gave similar promising results (entry 4) and will be exploited further on (*vide infra*). Further iterations (Table 2), including the use of classical, thermal conditions, lower Pd loadings, additives such as silver salts,[7] led to no or little improvement, although higher concentrations of reagents led to slightly improved conversions (entry 9, Table 2).

Using our "optimised" approach we synthesised a range of benzodiazepines *via* this last-stage C–H activation protocol. Critically, we were able to confirm that the C–H activation had occurred in the *ortho*-position as anticipated from a chelation controlled process by crystal-structure determinations of a number of products (*vide infra*)[8] (Figure 1). We synthesised a series of fluorinated aromatics **2** due to the advantageous role of fluorine in medicinal chemistry.[9]

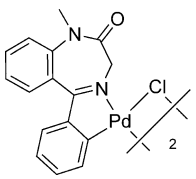
At this stage, we were still somewhat dissatisfied with this approach since we were confined to an N-1 methyl substituent in the final product. A broader diversity would be enabled by having a N-protected or free amide group, enabling further diversification after the arylation reaction. To test the more attractive latter hypothesis, preliminary studies on the C–H activation process were carried out (Scheme 2) and established that:

(i) Stoichiometric chelation-assisted C–H activation is indeed possible on the unsubstituted N–H amide since the palladacycle **3** can be isolated.
(ii) An attempted interception of the palladacycle intermediate, by a Pd-catalyzed H/D exchange,[10] did not lead to the expected product **1c**. Instead,

**Table 1.** Optimization of C–H activation.[a]




**1a** **2a**

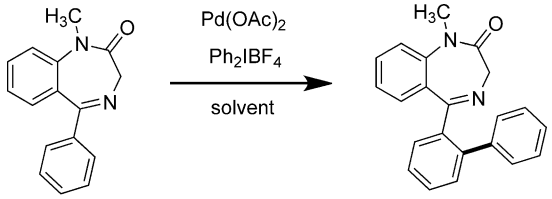
| Entry | R–X (equiv.) | Catalyst (mol%) | Time [h] | Temp. [°C] | Conversion by $^1$H NMR/LC-MS [%] | Solvent |
|---|---|---|---|---|---|---|
| 1 | $Ph_2IBF_4$ (1.5) | – | 1.5 | 125 | 0 | AcOH |
| 2 | **$Ph_2IBF_4$ (1.5)** | **$Pd(OAc)_2$ (5)** | **1.5** | **125** | **55** | **AcOH** |
| 3 | $Ph_2IBF_4$ (1.5) | $Pd(OAc)_2$ (5) | 1.5 | 125 | 5 | EtOAc |
| 4 | [Mes–I–Ar] OTf (1.5) | $Pd(OAc)_2$ (5) | 1.5 | 125 | 50 | AcOH |
| 5[b] | PhBr (1.5) | $Pd(OAc)_2$ (5) | 1 | 125 | 0 | AcOH |
| 6 | $Ph_2IBF_4$ (1.5) |  (5) | 1.5 | 125 | 22 | AcOH |
| 7 | $Ph_2IBF_4$ (2.5) | $(MeCN)_2PdCl_2$ (10) | 1.5 | 125 | 0 | AcOH |
| 8 | $Ph_2IBF_4$ (1.5) | $(MeCN)_2PdCl_2$ (5) | 1.5 | 125 | 0 | DCE |
| 9 | $Ph_2IBF_4$ (1.5) | $Pd(OAc)_2$ (2.5) | 1.5 | 125 | 0 | AcOH |



[a] All reactions were conducted in a CEM Explorer microwave unless stated otherwise. DCE = 1,2-dichloroethane; EtOAc = ethyl acetate.
[b] Conventional heating.

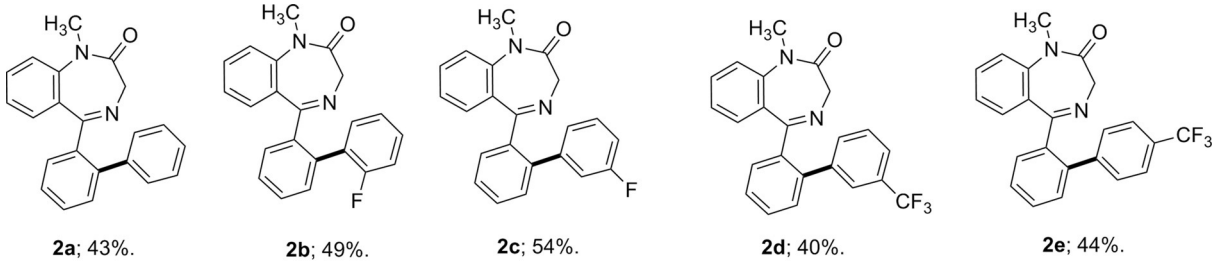
**Table 2.** Further reaction optimization studies.[a]



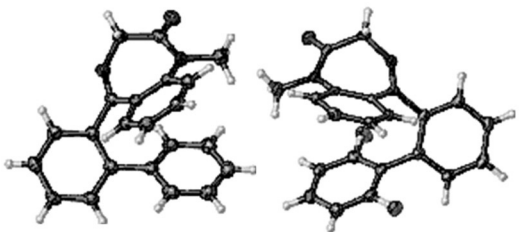

**1a** **2a**

| Entry | $Ph_2IBF_4$ [equiv.] | $Pd(OAc)_2$ [mol%] | Time [h] | Temp. [°C] | Conversion by NMR [%] | AcOH [mL] |
|---|---|---|---|---|---|---|
| 1[b] | 1.5 | 5 | 64 | 100 | 44 | 5 |
| 2[c] | 1.5 | 100 | 1.5 | 125 | 0 | 5 |
| 3 | 1.5 | 5 | 0.15 + 0.5 | 150 + 120 | 28 | 5 |
| 4 | 1.5 | 10 | 2 | 130 | 47 | 5 |
| 5 | 2.5 | 10 | 1 | 130 | 51 | 5 |
| 6 | 1.5 | 10 | 1 | 125 | 48 | 5 |
| 7 | 1.5 | 5 | 1.25 | 125 | 54 | 5 |
| 8 | 1.5 | 10 | 1.5 | 125 | 55 | 5 |
| 9 | **1.5** | **5** | **1** | **125** | **58** | **2.5** |
| 10[d] | 1.5 | 5 | 1 | 125 | 33 | 2.5 |
| 11[e] | 1.5 | 5 | 1 | 125 | 20 | 2.5 |
| 12[f] | 1.5 | 5 | 1 | 125 | 16 | 2.5 |
| 13[g] | 1.5 | 5 | 1 | 125 | 52 | 2.5 |
| 14[h] | 1.5 | 5 | 1 | 125 | 30 | 2.5 |

[a] All reactions were conducted in a CEM Explorer microwave unless stated otherwise.
[b] Conventional heating.
[c] Analysis of the crude mixture, after $PPh_3$ treatment, showed evidence that the palladacycle was formed.
[d] $Ag_2O$ added (1.5 equiv.).
[e] $Ag_2O$ added (1.5 equiv. at 100 °C).
[f] AgOAc added (1.5 equiv. at 100 °C).
[g] AcOH degassed, reaction under $N_2$.
[h] AcOH dry and degassed, reaction under $N_2$.




**2a**; 43%. **2b**; 49%. **2c**; 54%. **2d**; 40%. **2e**; 44%.

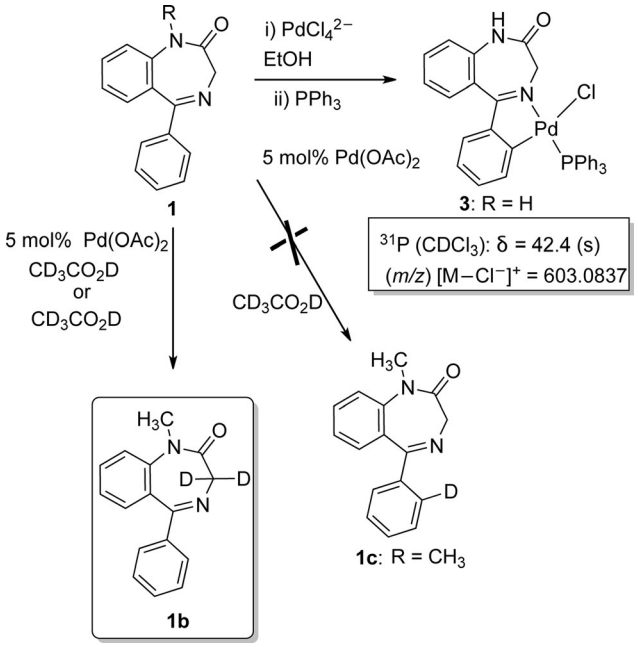


(for **2b**, note disorder and double occupancy for the fluoro substituent).

**Figure 1.** *ortho*-Arylated benzodiazepines.

this reaction, furnished uniquely the $D_2$-methylene compound **1d**, which could ***also be accomplished in the absence of the metal catalyst*** by merely stirring in deuterated acetic acid in the microwave, similar to previous findings on H/D exchange.[11]




**Scheme 2.** Deuteration and palladation reactions of **1**.

Next, we produced a library of benzodiazepines lacking an N-1 substituent (Figure 2). Of note, we were also able to produce arylated nordazepam[12] derivatives **5**; nordazepam was quickly made by an adaptation of a microwave protocol.[13] Yields, in general, were superior to those for their N-methylated analogues, mainly with electron-poor arenes, whereas the electron-rich **4f** and **4h** were made in moderate yield (note: the 2-tolyl derivative of **4h** did not form, possibly due to steric effects). We were pleasantly surprised to be able to obtain the hindered **4g**, albeit under more forcing microwave conditions. Analogue **5b** was made from a mesityl-containing aryliodonium salt.

Products were separated initially using a mass-triggered LC-MS protocol[14] but we found that a reversed-phase LC-MS method was equally useful and we were also able to recover traces of unreacted starting material. Moreover, diarylated products were often observed in the crude reaction mixtures and, in some cases, were isolated (Scheme 3, for example, **5c′**, **5d′**). The yields of **5d** and **5d′** were rather low, even when using a higher temperature.

Following our earlier studies (Scheme 2), we prepared a small number of deuterated derivatives **6a**–**6c** (Scheme 4). Compound **6a**, the deuterated analogue of **5c**, was prepared by a one-pot dual C–H activation/H–D exchange by simply carrying out the catalytic arylation protocol in $CD_3CO_2D$ whereas **6b**, **6c** (and earlier, **1b**) were simply prepared by stirring the arylated precursors in $CD_3CO_2D$ in a microwave.

Deuterated benzodiazepine products were easily characterized, for example, by $^2H$ NMR (see the Supporting Information, note: ND tends to revert to NH when the samples are concentrated in air).

A further illustration of the diversity achievable is that the resulting elaborated nordazepam derivatives **5** can be N-alkylated to afford substituted diazepam and pinazepam analogues (Figure 3).

## Conclusions

In summary, we have synthesized a library of benzodiazepines *via* a late stage C–H activation reaction. Studies are now underway to address the drug-likeness of the products by for example, lowering their clogP, testing their biological activity, as well as applying this chemistry to other systems related to benzodiazepines such as benzotriazepines.[15]

## Experimental Section

### General Information

All commercially purchased materials and solvents were used without further purification unless specified otherwise. NMR spectra were recorded on a Varian VNMRS 500 ($^1H$ 500 MHz, $^{13}C$ 126 MHz) and VNMRS 400 ($^{19}F$ 376 MHz, $^2H$ 61 MHz and $^{31}P$ 162 MHz) spectrometers and prepared in deuterated solvents such as $CDCl_3$ and DMSO-$d_6$. $^1H$ and $^{13}C$ chemical shifts were recorded in parts per million (ppm). Multiplicity of $^1H$ NMR peaks are indicated by s – singlet, d – doublet, dd – doublets of doublets, t – triplet, pt – pseudo triplet, q – quartet, m – multiplet and coupling constants are given in Hertz (Hz). Electron spray ionisation-high resolution mass spectra (ESI-HR-MS) were obtained using a Bruker Daltonics Apex III where Apollo ESI was used as the ESI source. All analyses were conducted by Dr. A. K. Abdul-Sada. The molecular ion peaks [M]+ were recorded in mass to charge ($m/z$) ratio.

LC-mass spectra were acquired using a Shimadzu LC-MS 2020, on a Gemini 5 m C18 110 Å. column. All X-ray analyses were performed at the UK National Crystallography Services, Southampton. All elemental analyses were carried out at the Elemental Analysis Service, London Metropolitan University. Purifications were performed by flash chromatography on silica gel columns or C18 columns using a Combi flash RF 75 PSI, ISCO unit.

CCDC 1422838, 1422839, 1422840, 1422841, 1422842, 1422843 and CCDC 1422844 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

### 1-Methyl-5-biphenyl-2-yl-1,3-dihydro-*2D*-1,4-benzodiazepin-2-one (1b)

Compound **2a** was stirred in acetic acid-$d_4$ at 125 °C in the microwave for 1 hour. Thereafter, the reaction mixture was cooled and the white product was collected in quantitative yield by evaporating the solvent. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 7.81–7.72$ (m, 1H), 7.56–7.45 (m, 2H), 7.27 (d,

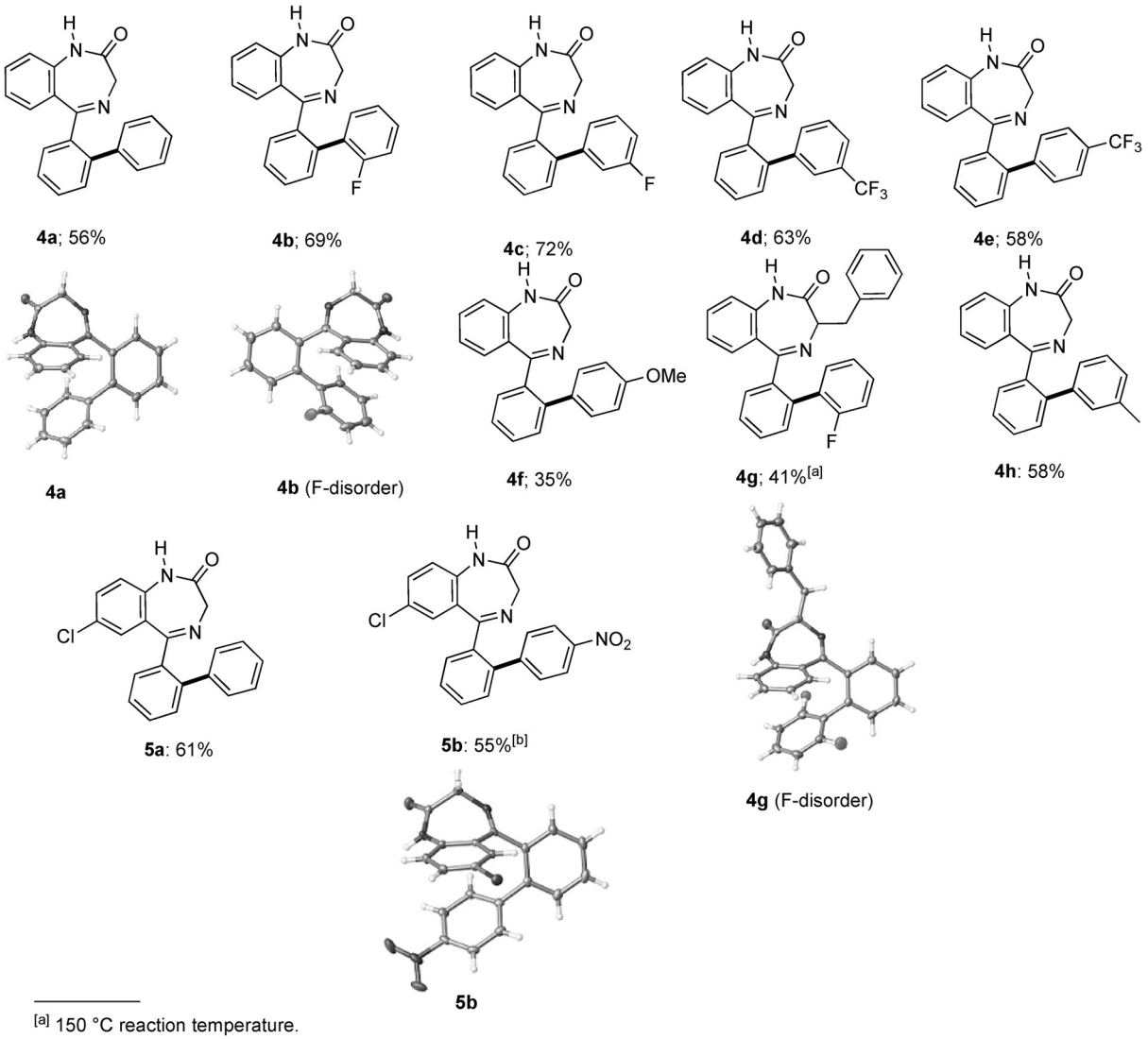


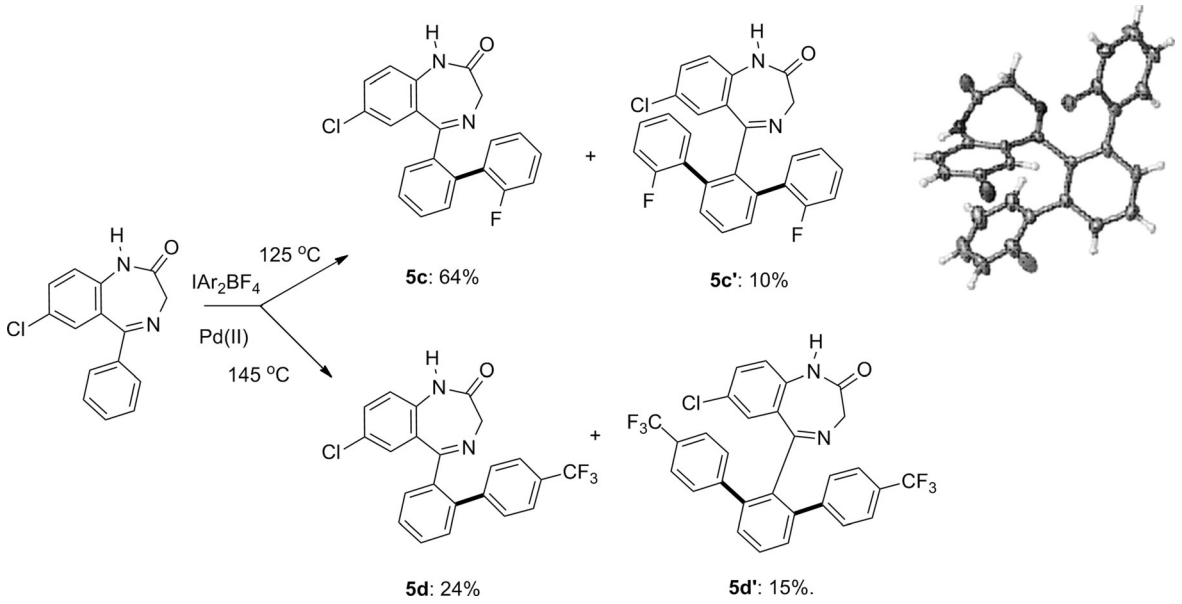

**Figure 2.** Arylation of 1-NH-benzodiazepines.

$J=7.6$ Hz, 1H), 7.22 (pt, $J=7.9$ Hz, 1H), 7.09–6.98 (m, 3H), 6.92–6.82 (m, 5H), 3.13 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta=173.2$, 169.4, 142.9, 142.2, 138.4, 131.2, 130.5, 130.2, 130.0, 129.9, 129.2, 128.7 (2C), 127.7 (2C), 127.5, 126.5, 123.4, 120.1, 55.5 (m), 34.9; $^2$H NMR (61 MHz. $CH_3CO_2H$): $\delta=4.95$ (1H), 3.94 (1H); HR-MS-ESI: $m/z=$ 329.1614, calculated for $C_{21}H_{16}D_2N_2O$ $[+H]^+$: 329.1617.

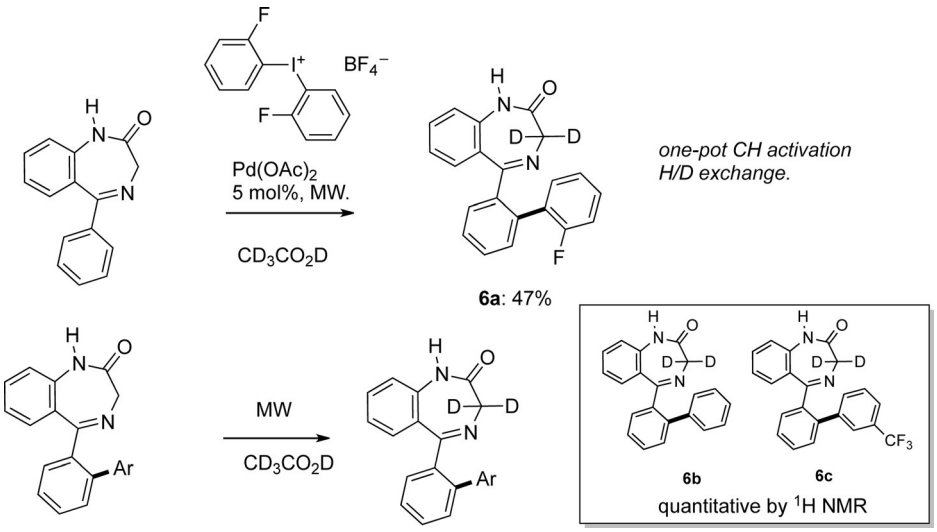
## 1-Methyl-5-biphenyl-2-yl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (2a)

1-Methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (0.15 g, 0.60 mmol), diphenyliodonium tetrafluoroborate (0.33 g, 0.90 mmol) and palladium(II) acetate (6.0 mg, 5 mol%) were combined in glacial acetic acid (4 mL) and stirred for 1 h at 125 °C in the microwave. Thereafter the cooled reaction mixture was filtered over celite, washed with dichloromethane (DCM, 10 mL) and concentrated under reduced pressure. The residue was dissolved in DCM (20 mL), washed with saturated sodium bicarbonate and the organic layer was collected using a (hydrophobic frit) phase separator. The solution was concentrated under reduced pressure to yield an orange product. The crude material was purified by flash chromatography (30 g C18, acetonitrile: water, 30% to 90%) and the final product was obtained as a white powder; yield: 0.083 g (43%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta=7.78$ (d, $J=7.9$ Hz, 1H), 7.57–7.49 (m, 2H), 7.29 (dd, $J=6.7$, 1.9 Hz, 1H), 7.26–7.20 (m, 1H), 7.11–7.20 (m, 3H), 6.93 (d, $J=6.4$ Hz, 2H), 6.91–6.85 (m, 3H), 4.83 (d, $J=$ 11.0 Hz, 1H), 3.73 (d, $J=11.0$ Hz, 1H), 3.15 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta=173.0$, 169.5, 139.5, 143.0, 142.1, 140.8, 138.6, 131.2, 130.5, 130.1, 130.0, 129.1, 128.7 (2C), 127.7 (2C), 127.5, 126.4, 123.3, 120.0, 56.3, 34.9; HR-MS-ESI: $m/z=327.1492$, calculated for $C_{22}H_{18}N_2O$ $[+H]^+$: 327.1497; elemental analysis: calculated for $C_{22}H_{18}N_2O$ (%): C 80.96, H 5.56, N 8.58; found: C 80.69, H 5.32, N 8.54.




**Scheme 3.** Nordazepam mono- and diarylations.




**Scheme 4.** Synthesis of deuterated elaborated benzodiazepines.

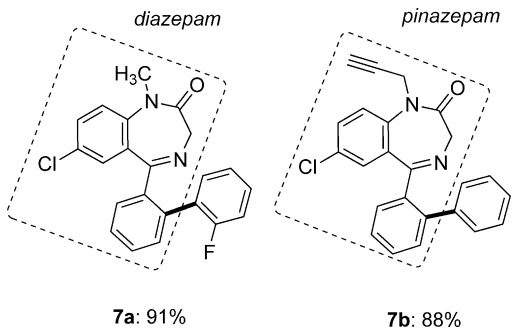



**Figure 3.** *ortho*-Arylated pharmaceuticals.

### 1-Methyl-5-(2′-fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (2b)

This was synthesised on a 0.31 mmol scale by the same procedure as **2a** and bis(2-fluorophenyl)iodonium tetrafluoroborate (0.18 g, 0.49 mmol) was used instead of diphenyliodonium tetrafluoroborate. The final product was obtained as a white powder; yield: 0.052 g (49%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 7.78$ (dd, $J = 5.8$, 3.4 Hz, 1H), 7.52 (dd, $J = 5.8$, 3.4 Hz, 2H), 7.31 (dd, $J = 5.5$ Hz, 3.5 Hz, 1H), 7.26–7.23 (m, 1H), 7.11–7.05 (m, 1H), 6.98 (dd, $J = 7.9$, 1.7 Hz, 1H), 6.96–6.92 (m, 2H), 6.91 (d, $J = 3.1$ Hz, 1H), 6.89 (d, $J = 2.2$ Hz, 1H), 6.72 (pt, $J = 9.0$ Hz, 1H), 4.78 (d, $J = 10.8$ Hz, 1H), 3.68 (d, $J = 10.8$ Hz, 1H), 3.14 (s, 3H); $^{13}$C NMR (126 MHz,

$CDCl_3$): $\delta = 171.7$, 170.3, 158.9 (d, $^1J_{F,C} = 247.3$ Hz), 142.8, 139.7, 135.6, 131.5 (d, $^3J_{F,C} = 3.1$ Hz), 130.8, 130.4, 129.9, 129.4, 129.1, 128.6 (d, $^3J_{F,C} = 8.0$ Hz), 128.5 (d, $^2J_{F,C} = 16.1$ Hz), 128.4, 128.1, 123.4, 123.3 (d, $^4J_{F,C} = 3.8$ Hz), 119.9, 115.0 (d, $^2J_{F,C} = 22.3$ Hz), 56.6, 35.0; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta = -115.1$ (1F); HR-MS-ESI: $m/z =$ 345.1390, calculated for $C_{22}H_{17}FN_2O$ $[+H]^+$: 345.1398; elemental analysis: calculated for $C_{22}H_{17}FN_2O$ (%): C 76.73, H 4.98, N 8.13; found: C 76.59, H 4.82, N 8.26.

### 1-Methyl-5-(3′-fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (2c)

The same procedure as **2a** was used but bis(3-fluorophenyl)-iodonium tetrafluoroborate (0.36 g, 0.90 mmol) was used instead of diphenyliodonium tetrafluoroborate. The final product was obtained as a white powder; yield: 0.111 g (54%). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 7.70$ (d, $J = 7.4$ Hz, 1H), 7.64–7.55 (m, 2H), 7.35 (d, $J_{F,H} = 7.4$ Hz, 2H), 7.18–7.13 (m, 2H), 6.96 (pt, $J = 7.8$ Hz, 2H), 6.74 (d, $J = 7.8$ Hz, 1H), 6.71 (d, $J_{F,H} = 7.7$ Hz, 1H), 6.67 (d, $J = 10.0$ Hz, 1H), 4.55 (d, $J = 11.0$ Hz, 1H), 3.69 (d, $J = 11.0$ Hz, 1H), 3.10 (s, 3H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): $\delta = 172.3$, 168.9, 162.1 (d, $^1J_{F,C} = 244.9$ Hz), 143.1 (d, $^3J_{F,C} = 11.9$ Hz), 140.5, 138.6, 132.1, 131.1, 130.4, 130.4 (d, $^3J_{F,C} = 4.3$ Hz), 130.3, 129.4, 129.1, 128.3, 125.0, 124.0, 121.1, 115.5 (d, $^2J_{F,C} = 21.8$ Hz), 114.0 (d, $^2J_{F,C} = 20.9$ Hz), 114.1, 56.6, 34.8; $^{19}$F NMR (376 MHz, DMSO-$d_6$): $\delta = -113.4$ (1F); HR-MS-ESI: $m/z = 345.1394$, calculated for $C_{22}H_{17}FN_2O$ $[+H]^+$: 345.1398; LC-MS: purity (UV) = 96%, retention time (tR) = 15.13 min.

### 1-Methyl-5-(3′-trifluoromethylbiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (2d)

The same procedure as **2a** was used but bis(3-trifluoromethylphenyl)iodonium tetrafluoroborate (0.45 g, 0.90 mmol) was used instead of diphenyliodonium tetrafluoroborate. The final product was obtained as a white powder; yield: 0.095 g (40%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 7.79$–$7.74$ (m, 1H), 7.57–7.53 (m, 2H), 7.36 (d, $J = 7.7$ Hz, 1H), 7.26–7.23 (m, 2H), 7.21 (d, $J = 7.7$ Hz, 1H), 7.17 (d, $J = 1.6$ Hz, 1H), 7.16–7.14 (m, 1H), 6.94–6.85 (m, 3H), 4.81 (d, $J = 10.9$ Hz, 1H), 3.69 (d, $J = 10.9$ Hz, 1H), 3.10 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta = 172.0$, 169.7, 142.8, 141.9, 140.6, 139.1, 132.3, 131.2, 130.4, 130.6, 130.0 (q, $^2J_{F,C} = 29.9$ Hz), 129.9, 129.8, 129.1, 128.1, 127.9, 125.2 (q, $^3J_{F,C} = 3.2$ Hz), 123.7 (q, $^1J_{F,C} = 272.9$ Hz), 123.4, 123.1 (q, $^3J_{F,C} = 3.8$ Hz), 119.9, 56.7, 34.7; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta = -63.3$ (s, 3F); HR-MS-ESI: $m/z = 395.1381$, calculated for $C_{23}H_{17}F_3N_2O$ $[+H]^+$: 395.1366; LC-MS: purity (UV) = 95%, tR = 18.14 min.

### 1-Methyl-5-(4′-trifluoromethylbiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (2e)

The same procedure as **2a** was used but bis(4-trifluoromethylphenyl)iodonium tetrafluoroborate (0.45 g, 0.90 mmol) was used instead of diphenyliodonium tetrafluoroborate. The final product was obtained as a white powder; yield: 0.104 g (44%). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 7.72$–$7.68$ (m, 1H), 7.61–7.58 (m, 2H), 7.48 (d, $J = 7.9$ Hz, 2H), 7.37–7.28 (m, 2H), 7.12–7.05 (m, 3H), 6.97–6.90 (m, 1H), 6.74 (dd, $J = 7.9$, 1.6 Hz, 1H), 4.54 (d, $J = 10.9$ Hz, 1H), 3.64 (d, $J = 10.9$ Hz, 1H), 3.04 (s, 3H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): $\delta = 171.6$, 169.2, 145.0, 143.1, 140.3, 139.2, 131.8, 131.0, 130.4, 130.2, 129.7, 129.5 (2C), 128.9, 128.6, 127.6 (q, $^2J_{F,C} = 31.6$ Hz), 125.1 (q, $^3J_{F,C} = 3.7$ Hz, 2C), 124.6 (q, $^1J_{F,C} = 272$ Hz), 123.9, 120.8, 56.9, 34.7; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta = -61.15$ (s, 3F); HR-MS-ESI: $m/z = 395.1374$, calculated for $C_{23}H_{17}F_3N_2O$ $[+H]^+$: 395.1366; elemental analysis: calculated for $C_{23}H_{17}F_3N_2O$ (%): C 70.04, H 4.34, N 7.10; found: C 69.95, H 4.38, N 6.98.

### Palladacycle (3)

5-Phenyl-1*H*-1,4-diazepin-2(3*H*)-one (0.20 g, 0.85 mmol) and sodium tetrachloropalladate (0.23 g, 0.78 mmol) were combined in ethanol (20 mL) for 48 h at room temperature. The orange precipitate was filtered and washed with further ethanol (10 mL) and chloroform (10 mL). An orange solid powder was collected after drying under vacuum; yield: 0.25 g (69%). The product was too insoluble for NMR analysis.

The product from above reaction (0.12 g, 0.33 mmol) and triphenylphosphine (0.08 g, 0.30 mmol) were combined in dichloromethane (10 mL) and stirred overnight. The resulting unwanted precipitate was filtered through celite and the filtrate was concentrated under vacuum. Hexane was added to the concentrated crude product to induce precipitation, the precipitates was filtered and dried under vacuum. The product was obtained as a yellow solid; yield: 0.12 g (63%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 9.29$ (s, 1H), 7.81–7.75 (m, 6H), 7.72 (d, $J = 8.4$ Hz, 2H), 7.59 (pt, $J = 7.8$ Hz, 1H), 7.44–7.41 (m, 3H), 7.39–7.34 (m, 5H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.04 (d, $J = 7.7$ Hz, 1H), 6.83 (pt, $J = 7.3$ Hz, 1H), 6.57–6.49 (m, 2H), 6.15 (d, $J = 12.2$ Hz, 1H), 3.81 (d, $J = 12.2$ Hz, 1H); $^{13}$C NMR (500 MHz) $CDCl_3$: $\delta = 182.3$, 171.6, 159.1, 147.8, 138.6, 135.5 (2C), 135.4 (4C), 135.0 (2C), 132.5, 131.4, 131.2, 131.0, 130.9, 130.6 (2C), 130.4, 130.2, 128.0 (4C), 127.9 (2C), 124.3, 123.5, 123.4, 121.9, 53.9; $^{31}$P NMR (162 MHz $CDCl_3$): $\delta = 42.4$ (s, 1P); HR-MS-ESI: $m/z = 603.0837$, calculated for $C_{33}H_{26}ClN_2OPPd$ $[-Cl^-]^+$: 603.0812; elemental analysis: calculated for $C_{33}H_{26}ClN_2OPPd \cdot 0.9\,CH_2Cl_2$ (%): C 56.88, H 3.91, N 3.91; found: C 56.69, H 4.02, N 3.84.

### 5-Phenyl-5-biphenyl-2-yl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (4a)

5-Phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (0.14 g, 0.59 mmol), diphenyliodonium tetrafluoroborate (0.33 g, 0.90 mmol) and palladium (II) acetate (6.0 mg, 5 mol%) were combined in degassed glacial acetic acid (4 mL) and stirred for 1 h at 125 °C. Thereafter the cooled reaction mixture was filtered over celite, washed with DCM (10 mL) and concentrated under reduced pressure. The residue was dissolved in DCM (20 mL), washed with saturated sodium bicarbonate and the organic layer was collected using a (hydrophobic frit) phase separator. The solution was concentrated under reduced pressure to yield an orange product. The crude material was purified by flash chromatography (30 g C18, acetonitrile: water, 30% to 90%). Starting material, 5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one was recovered (0.031 g, 0.13 mmol) and the final product was obtained as a white powder; yield: 0.079 g (56%). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 10.33$ (s, 1H), 7.57 (dd, $J = 7.1$,

1.8 Hz, 1H), 7.55 (dd, $J=7.5$, 1.6 Hz, 1H), 7.52–7.47 (m, 1H), 7.34 (dd, $J=7.6$, 1.4 Hz, 1H), 7.19–7.14 (m, 1H), 7.12–7.04 (m, 3H), 6.95–6.90 (m, 2H), 6.79 (dd, $J=7.9$, 6.4 Hz, 2H), 6.74–6.70 (m, 1H), 4.04 (s, 2H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): $\delta=172.3$, 169.7, 141.5, 140.5, 139.8, 139.2, 131.3, 130.9, 130.2, 130.1, 129.4, 128.6 (2C), 128.3, 128.0 (2C), 127.6, 127.1, 122.6, 120.7, 57.3; HR-MS-ESI: $m/z=313.1336$, calculated for $C_{21}H_{16}N_2O$ $[+H]^+$: 313.1335; elemental analysis: calculated for $C_{21}H_{16}N_2O$ (%): C 80.75, H 5.16, N 8.97; found: C 80.64, H 5.06, N 9.08.

### 5-(2′-Fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (4b)

The same method as **4a** was used but bis(2-fluorophenyl)iodonium tetrafluoroborate (0.36 g, 0.90 mmol) was used instead of diphenyliodonium tetrafluoroborate. Starting material, 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, was recovered (0.021 g, 0.09 mmol) and the final product was obtained as a white powder; yield: 0.114 g (69%). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta=10.25$ (s, 1H), 7.59–7.49 (m, 3H), 7.35–7.30 (m, 1H), 7.22 (ddd, $J=6.7$, 2.0 Hz, $^3J_{F,H}=8.4$ Hz, 1H), 7.16–7.10 (m, 1H), 6.97–6.87 (m, 3H), 6.86–6.85 (m, 2H), 6.83 (d, $J=8.2$ Hz, 1H), 3.97 (s, 2H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): $\delta=175.9$, 174.6, 163.4 (d, $^1J_{F,C}=247.3$ Hz), 145.3, 143.8, 140.3, 136.2 (d, $^4J_{F,C}=3.2$ Hz), 136.1, 135.8, 135.4, 134.5, 134.4 (t, $^3J_{F,C}=4.1$ Hz), 133.1, 132.9 (d, $^2J_{F,C}=15.6$ Hz), 132.7, 128.9 (d, $^3J_{F,C}=3.5$ Hz), 127.4, 125.5, 120.1, 120.0 (d, $^2J_{F,C}=22.1$ Hz), 62.1; $^{19}$F NMR (376 MHz, DMSO-$d_6$): $\delta=-113.4$ (1F); HR-MS-ESI: $m/z=331.1232$, calculated for $C_{21}H_{15}FN_2O$ $[+H]^+$: 331.1241; elemental analysis: calculated for $C_{21}H_{15}FN_2O$ (%): C 76.35, H 4.58, N 8.48; found: C 76.23, H 4.68, N 8.47.

### 5-(3′-Fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (4c)

The same method as **4a** was used but bis(3-fluorophenyl)iodonium tetrafluoroborate (0.36 g, 0.90 mmol) was used instead of diphenyliodonium tetrafluoroborate. Starting material, 5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one was recovered (0.045 g, 0.19 mmol) and the final product was obtained as a white powder; yield: 0.095 g (72%). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta=10.36$ (s, 1H), 7.59 (dd, $J=1.8$, $^3J_{F,H}=7.2$ Hz, 1H), 7.56 (dd, $J=7.4$, 1.7 Hz, 1H), 7.54 (dd, $J=7.4$, 1.5 Hz, 1H), 7.36 (dd, $J=7.5$, 1.5 Hz, 1H), 7.21 (ddd, $J=8.5$, 1.6, $^3J_{F,H}=7.1$ Hz, 1H), 7.15–7.10 (m, 1H), 6.92–6.87 (m, 1H), 6.86–6.80 (m, 2H), 6.73 (dd, $J=7.7$, 1.6 Hz, 2H), 6.70 (d, $J=10.0$ Hz, 1H), 4.05 (s, 2H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): $\delta=172.0$, 169.8, 161.8 (d, $^1J_{F,C}=243.9$ Hz), 142.9 (d, $^3J_{F,C}=8.0$ Hz), 140.2, 139.8, 139.3, 131.5, 130.9, 130.2, 130.1, 129.9 (d, $^3J_{F,C}=8.4$ Hz), 129.5, 128.2, 128.1, 124.9, 122.7, 120.6, 115.3 (d, $^2J_{F,C}=21.9$ Hz), 113.9 (d, $^2J_{F,C}=21.0$ Hz), 57.3; $^{19}$F NMR (376 MHz, DMSO-$d_6$): $\delta=-113.4$ (1F); HR-MS-ESI: $m/z=331.1239$, calculated for $C_{21}H_{15}FN_2O$ $[+H]^+$: 331.1241; LC-MS: purity (UV) = 100%, tR = 12.19 min.

### 5-(3′-Trifluoromethylbiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (4d)

The same method as **4a** was used but bis(3-trifluoromethylphenyl)iodonium tetrafluoroborate (0.45 g, 0.90 mmol) was used instead of diphenyliodonium tetrafluoroborate. Starting material, 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, was recovered (0.022 g, 0.09 mmol) and the final product was obtained as a white powder; yield: 0.119 g (63%). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta=10.22$ (s, 1H), 7.63–7.53 (m, 3H), 7.42 (d, $J=7.9$ Hz, 1H), 7.38 (dd, $J=7.4$, 1.5 Hz, 1H), 7.34 (pt, $J=7.9$ Hz, 1H), 7.20–7.14 (m, 3H), 6.85–6.79 (m, 2H), 6.75 (dd, $J=8.2$, 1.5 Hz, 1H), 4.03 (s, 2H); $^{13}$C NMR (126 MHz, DMSO-$d_6$: $\delta=171.7$, 169.8, 141.6, 140.1, 139.9, 139.2, 132.6, 131.5, 130.9, 130.2 (2C), 129.6, 129.1, 129.0 (q, $^2J_{F,C}=31.8$ Hz), 128.4, 128.0, 125.0 (q, $^3J_{F,C}=3.7$ Hz), 124.3 (q, $^1J_{F,C}=272.6$ Hz), 123.8 (q, $^3J_{F,C}=3.7$ Hz), 122.6, 120.6, 57.4; $^{19}$F NMR (376 MHz, DMSO-$d_6$): $\delta=-61.2$ (s, 3F): HR-MS-ESI: $m/z=381.1211$, calculated for $C_{22}H_{15}F_3N_2O$ $[+H]^+$: 381.1209; elemental analysis: calculated for $C_{22}H_{15}F_3N_2O\cdot0.3\,CH_2Cl_2$ (%): C 66.00, H 3.87, N 6.90; found: C 66.19, H 3.97, N 6.99.

### 5-(4′-Trifluoromethylbiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (4e)

The same method as **4a** was used but bis(4-trifluoromethylphenyl)iodonium tetrafluoroborate (0.45 g, 0.90 mmol) was used instead of diphenyliodonium tetrafluoroborate. Starting material, 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, was recovered (0.036 g, 0.15 mmol) and the final product was obtained as a white powder; yield: 0.097 g (58%). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta=10.46$ (s, 1H), 7.62 (pt, $J=6.7$ Hz, 2H), 7.59–7.53 (m, 1H), 7.44 (d, $J=7.9$ Hz, 2H), 7.40 (d, $J=7.5$ Hz, 1H), 7.18 (pt, $J=7.6$ Hz, 1H), 7.13 (d, $J=7.8$ Hz, 2H), 6.80 (d, $J=7.8$ Hz, 2H), 6.75 (d, $J=7.9$ Hz, 1H), 4.05 (s, 2H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): $\delta=171.7$, 169.9, 144.6, 140.1, 139.7, 139.3, 131.5, 131.2, 130.4, 130.3, 129.5, 129.4 (2C), 128.5, 128.1, 127.7 (q, $^2J_{F,C}=31.6$ Hz), 124.9 (q, $^3J_{F,C}=4.1$ Hz, 2C), 124.6 (q, $^1J_{F,C}=272.8$ Hz), 122.8, 120.6, 57.3; $^{19}$F NMR (376 MHz, DMSO-$d_6$): $\delta=-61.0$ (s, 3F); HR-MS-ESI: $m/z=381.1206$, calculated for $C_{22}H_{15}F_3N_2O$ $[+H]^+$: 381.1209; elemental analysis: calculated for $C_{22}H_{15}F_3N_2O$ (%): C 69.47, H 3.98, N 7.36; found: C 69.30, H 3.88, N 7.44.

### 5-(4′-Methoxybiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (4f)

The same method as **4a** was used but 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (0.095 g, 0.40 mmol) and bis(4-methoxyphenyl)iodonium tetrafluoroborate (0.26 g, 0.60 mmol) were used instead of diphenyliodonium tetrafluoroborate. Starting material, 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one was recovered (0.016 g, 0.07 mmol) and the final product was obtained as a white powder; yield: 0.039 g (35%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta=8.36$ (s, 1H), 7.69 (d, $J=7.4$ Hz, 1H), 7.53–7.42 (m, 2H), 7.28 (d, $J=7.5$ Hz, 1H), 7.16 (pt, $J=7.7$ Hz, 1H), 6.94–6.80 (m, 4H), 6.70 (d, $J=8.1$ Hz, 1H), 6.61 (d, $J=8.1$ Hz, 2H), 4.30 (s, 2H), 3.72 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta=173.2$, 170.5, 158.6, 141.6, 137.3, 133.3, 131.2, 130.0, 130.1, 129.9, 129.8 (2C), 129.7, 129.6, 127.0, 123.2, 120.0, 113.1 (2C), 110.0, 56.3, 55.3; HR-MS-ESI: $m/z=343.1447$, calculated for $C_{22}H_{18}N_2O$ $[+H]^+$: 343.1441; LC-MS: purity (UV) = 99%, tR = 10.49 min.

### 3-Benzyl-5-(2′-fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (4g)

The same method as **4a** was used but 3-benzyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (0.17 g, 0.52 mmol) instead of 5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, and bis(2-fluorophenyl)iodonium tetrafluoroborate (0.29 g, 0.78 mmol) were used instead of diphenyliodonium tetrafluoroborate and the reaction was carried out at 150 °C. The final product was obtained as a white powder; yield: 0.090 g (41%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 7.83$ (s, 1H), 7.57–7.43 (m, 3H), 7.37–7.24 (m, 5H), 7.24–6.87 (m, 7H), 6.73 (pt, $J = 9.1$ Hz, 1H), 6.64 (d, $J = 8.0$ Hz, 1H), 3.75–3.54 (m, 2H), 3.35–3.40 (m, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta =$ 170.3, 170.1, 158.8 (d, $^1J_{F,C} = 247.1$ Hz), 139.9, 139.2, 136.8, 135.8, 131.7, 131.2, 130.8, 130.5, 129.9, 129.8 (2C), 129.5, 128.9 (d, $^3J_{F,C} = 8.2$ Hz), 128.5 (d, $^3J_{F,C} = 4.0$ Hz), 128.4, 128.3, 128.2 (2C), 128.1, 126.1, 123.3, 120.0, 114.9 (d, $^2J_{F,C} =$ 21.8 Hz), 64.8, 37.4; $^{19}$F NMR (376 MHz, DMSO-$d_6$): $\delta =$ −115.9 (s, 1F); HR-MS-ESI: $m/z = 421.1709$, calculated for $C_{28}H_{21}FN_2O$ [+H]$^+$: 421.1711; elemental analysis: calculated for $C_{28}H_{21}FN_2O$ (%): C 79.98, H 5.13, N 6.66; found: C 79.85, H 4.97, N 6.73.

### 5-(3′-Methylbiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (4h)

The same method as **4a** was used but 5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (0.100 g, 0.42 mmol) and (3-methylphenyl)(2,4,6-trimethylphenyl)iodonium triflate (0.31 g, 0.62 mmol) were used instead of diphenyliodonium tetrafluoroborate. Starting material, 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one was recovered (0.012 g, 0.05 mmol) and the final product was obtained as a white powder; yield: 0.070 g (58%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 8.41$ (s, 1H), 7.71 (dd, $J = 8.0$, 1.9 Hz, 1H), 7.53–7.45 (m, 2H), 7.31–7.28 (m, 1H), 7.17–7.12 (m, 1H), 6.96–6.91 (m, 1H), 6.88–6.81 (m, 3H), 6.78–6.73 (m, 2H), 6.67 (dd, $J = 8.0$, 1.0 Hz, 1H), 4.29 (s, 2H), 2.18 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta = 173.2$, 170.7, 142.2, 140.6, 139.6, 137.4, 137.1, 131.0, 129.9, 129.8, 129.7, 129.6, 129.5, 128.8, 127.4, 127.3, 127.2, 125.8, 123.0, 119.9, 56.4, 21.1; HR-MS-ESI: $m/z =$ 327.1483, calculated for $C_{22}H_{18}N_2O$ [+H]$^+$: 327.1492; elemental analysis: calculated for $C_{22}H_{18}N_2O$ (%): C 80.96, H 5.56, N 8.5; found: C 80.93, H 5.42, N 8.65.

### 7-Chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (Nordazepam)

5-Chloro-2-aminobenzophenone (0.621 g, 3.15 mmol), *N*-(3-dimethylaminpropyl)-*N*-ethylcarbodiimide hydrochloride (0.604 g, 3.15 mmol) and N-Boc-glycine (0.550 g, 3.15 mmol) were combined in toluene (6 mL) and irradiated in the microwave for 30 min at 150 °C. Trifluoroacetic acid (2 mL) was then added to the mixture and it was irradiated for a further 20 min at 150 °C. The cooled solution was neutralized by an aqueous 3N NaOH solution (50 mL) and extracted with dichloromethane (3 × 30 mL). The organic layers were dried over $MgSO_4$ and evaporated. The crude material was purified by column chromatography (ethyl acetate:DCM, 10% to 40%) and the final product was obtained as a white powder; 0.29 g (34%). $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 9.41$ (s, 1H), 7.53 (d, $J = 7.6$ Hz, 2H), 7.50–7.44 (m, 2H), 7.41 (pt, $J = 7.5$ Hz, 2H), 7.30 (d, $J = 2.4$ Hz, 1H), 7.14 (d, $J = 8.6$ Hz, 1H), 4.33 (s, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta = 171.7$, 169.8, 138.7, 137.3, 131.8, 130.7, 130.6, 129.6 (2C), 128.9, 128.5, 128.4 (2C), 122.6, 56.5; HR-MS-ESI: $m/z = 271.0627$, calculated for $C_{15}H_{11}ClN_2O$ [+H]$^+$: 271.0633; LC-MS: purity (UV) = 100%, tR = 12.40 min.

### 7-Chloro-5-biphenyl-2-yl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (5a)

The same method as **4a** was used but 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (0.16 g, 0.6 mmol) was used instead of 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one. Starting material, 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, was recovered (0.010 g, 0.04 mmol) and the final product was obtained as a white powder; yield: 0.118 g (61%). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 10.44$ (s, 1H), 7.63 (dd, $J = 7.6$, 1.5 Hz, 1H), 7.61–7.57 (m, 1H), 7.54–7.50 (m, 1H), 7.36 (dd, $J = 7.6$, 1.4 Hz, 1H), 7.21 (dd, $J = 8.7$, 2.5 Hz, 1H), 7.12 (dd, $J = 8.1$, 6.5 Hz, 2H), 7.10–7.05 (m, 1H), 6.91 (dd, $J = 7.2$, 1.7 Hz, 2H), 6.78 (d, $J = 8.7$ Hz, 1H), 6.63 (d, $J = 2.4$ Hz, 1H), 4.09 (s, 2H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): $\delta = 170.8$, 169.4, 141.6 140.5, 139.0, 138.2, 131.2, 131.1, 130.5, 130.3, 129.6, 128.5 (2C), 128.4, 128.2 (2C), 127.8, 127.2, 126.4, 122.7, 57.4; HR-MS-ESI: $m/z = 347.0947$, calculated for $C_{21}H_{15}ClN_2O$ [+H]$^+$: 347.0946; elemental analysis: calculated for $C_{21}H_{15}ClN_2O$ (%): C 72.73, H 4.36, N 8.08; found: C 72.63, H 4.26, N 8.15.

### 7-Chloro-5-(4′-nitrobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (5b)

The same method as for **5a** was used but (4-nitrophenyl)-(2,4,6-trimethylphenyl)iodonium triflate (0.47 g, 0.9 mmol) was used instead of of diphenylliodonium tetrafluoroborate. Starting material, 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one recovered (0.040 g, 0.15 mmol) and the final product was obtained as a white powder; yield: 0.099 g (55%). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 10.51$ (s, 1H), 8.08–7.91 (m, 3H), 7.70–7.65 (m, 1H), 7.64–7.61 (m, 1H), 7.44–7.40 (m, 1H), 7.27 (dd, $J = 8.8$, 2.6 Hz, 1H), 7.18–7.13 (m, 2H), 6.76 (d, $J = 8.8$ Hz, 1H), 6.69 (d, $J = 2.6$ Hz, 1H), 4.09 (s, 2H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): $\delta = 170.1$, 169.4, 144.6, 140.1, 139.6, 139.1, 138.1, 131.5, 131.1, 130.7, 130.1, 129.9, 129.7, 129.1, 128.6, 126.7, 125.4, 124.9, 123.8, 122.6, 57.4; HR-MS-ESI: $m/z = 392.0008$, calculated for $C_{21}H_{14}N_3O_3$ [+H]$^+$: 392.0013; LC-MS: purity (UV) = 94%, tR = 17.03 min.

### 7-Chloro-5-(2′-fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (5c)

The same method as **5a** was used but bis(2-fluoropheny)liodonium tetrafluoroborate (0.36 g, 0.9 mmol) was used instead of diphenylliodonium tetrafluoroborate. Starting material, 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, was recovered (0.010 g, 0.04 mmol), the final product as a white powder; yield: 0.13 g (64%) and the diarylated product **5c′** was collected as a white powder; yield: 0.026 g (10%). $^1$H NMR (500 MHz, DMSO-$d_6$: $\delta = 10.37$ (s, 1H), 7.66–7.61 (m, 1H), 7.59–7.54 (m, 2H), 7.34 (d, $J = 7.3$ Hz, 1H), 7.31–7.23 (m, 1H), 7.21–7.11 (m, 1H), 6.97 (pt, $J =$ 7.5 Hz, 1H), 6.91 (d, $J = 9.5$ Hz, 1H), 6.87 (dd, $J = 6.8$ Hz,

$^{3}J_{F,H}$=8.6 Hz, 1H), 6.82 (d, $J$=8.6 Hz, 1H), 6.76 (d, $J$=2.5 Hz, 1H), 4.03 (s, 2H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): $\delta$=169.8, 169.5, 158.7 (d, $^{1}J_{F,C}$=244.8 Hz), 139.82, 138.1, 135.5, 131.4, 131.2, 131.1, 130.9, 130.2, 129.8 (d, $^{3}J_{F,C}$=8.0 Hz), 129.6, 129.2, 128.6 (d, $^{3}J_{F,C}$=9.8 Hz), 128.0 (d, $^{2}J_{F,C}$=15.6 Hz), 126.6, 124.3 (d, $^{4}J_{F,C}$=3.5 Hz), 122.7, 115.3 (d, $^{2}J_{F,C}$=22.1 Hz), 57.3; $^{19}$F NMR (376 MHz, DMSO-$d_6$): $\delta$=−120.4 (1F); HR-MS-ESI: $m/z$=365.0847, calculated for $C_{21}H_{14}FN_2O$ [+H]$^+$: 365.0851; elemental analysis: calculated for $C_{21}H_{14}FN_2O$ (%): C 69.14, H 3.87, N 7.68; found: C 68.93, H 3.70, N 7.64.

**7-Chloro-5-(2,2′-difluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (5c′):** $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta$=7.77 (s, 1H), 7.59 (pt, $J$=7.7 Hz, 1H), 7.44 (d, $J$=7.7 Hz, 2H), 7.26–7.00 (m, 8H), 6.87 (pt, $J$=9.2 Hz, 2H), 6.49 (d, $J$=8.6 Hz, 1H), 3.85 (s, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$=168.3, 167.7, 159.0 (d, $^{1}J_{F,C}$=243.8 Hz, 2C), 139.0, 137.9, 136.4, 131.9, 131.8, 131.1 (2C), 131.0 (2C), 129.9 (d, $^{3}J_{F,C}$=8.1 Hz, 2C), 129.5, 129.3, 128.5, 128.3, 128.2, 126.5, 124.3 (d, $^{4}J_{F,C}$=3.5 Hz, 2C), 122.6, 115.4 (d, $^{2}J_{F,C}$=22.1 Hz, 2C), 56.9; $^{19}$F NMR (376 MHz, DMSO-$d_6$): $\delta$=−113.7 (2F); HR-MS-ESI: $m/z$=415.1072, calculated for $C_{27}H_{17}ClF_2N_2O$ [+H]$^+$: 459.1070; LC-MS: purity (UV)=97%, tR=20.38 min.

## 7-Chloro-5-(4′-trifluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (5d)

The same method as **5a** was used but diphenyliodonium tetrafluoroborate (0.45 g, 0.9 mmol) was used instead of diphenyliodonium tetrafluoroborate and the reaction temperature was 145 °C. Starting material, 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one, was recovered (0.020 g, 0.066 mmol) and the final product **5d** was obtained as a white powder; yield: 0.053 g (24%). The diarylated product **5d′** was collected as a brown powder; yield: 0.045 g (15%). $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta$=8.27 (s, 1H), 7.76 (d, $J$=7.0 Hz, 1H), 7.59 (dd, $J$=6.7, 6.0 Hz, 2H), 7.38 (d, $J$=7.8 Hz, 2H), 7.33 (d, $J$=7.0 Hz, 1H), 7.11 (d, $J$=7.9 Hz, 3H), 6.82 (s, 1H), 6.59 (d, $J$=8.6 Hz, 1H), 4.30 (s, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$=171.1, 170.1, 144.5, 140.6, 138.9, 136.0, 131.4, 130.4, 130.3, 129.8, 129.2, 129.0 (q, $^{2}J_{F,C}$=33.0 Hz), 129.0 (2C), 128.7, 128.4, 124.5 (q, $^{3}J_{F,C}$=3.7 Hz, 2C), 124.0 (q, $^{1}J_{F,C}$=272.4 Hz), 121.3, 121.2, 56.4; $^{19}$F NMR (376 MHz, DMSO-$d_6$: $\delta$=−63.2 (s, 3F); HR-MS-ESI: $m/z$=415.0819, calculated for $C_{22}H_{14}ClF_3N_2O$ [+H]$^+$: 415.0820; LC-MS: purity (UV)=95%, tR=19.59 min.

**7-Chloro-5-(4,4″-trifluorobiphenyl-2,6-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (5d′):** $^{1}$H NMR (500 MHz, DMSO-$d_6$): $\delta$=10.43 (s, 1H), 7.69 (pt, $J$=7.7 Hz, 1H), 7.57 (d, $J$=8.0 Hz, 4H), 7.50 (d, $J$=7.7 Hz, 2H), 7.30 (d, $J$=8.0 Hz, 4H), 7.26 (d, $J$=8.8 Hz, 1H), 6.91 (d, $J$=2.4 Hz, 1H), 6.72 (d, $J$=8.8 Hz, 1H), 3.71 (s, 2H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): $\delta$=168.4, 168.3, 145.0, 141.1, 138.3, 137.4, 131.6, 130.6 (2C), 130.2, 129.9 (4C), 129.6, 128.4, 127.9 (q, $^{2}J_{F,C}$=33.0 Hz, 2C), 126.7, 125.1 (q, $^{3}J_{F,C}$=3.7 Hz, 4C), 124.6 (q, $^{1}J_{F,C}$=270.4 Hz, 2C), 122.5, 120.0, 118.8, 56.9; $^{19}$F NMR (376 MHz, DMSO-$d_6$): $\delta$=−65.2 (s, 6F); HR-MS-ESI: $m/z$=559.1003, calculated for $C_{29}H_{17}ClF_6N_2O$ [+H]$^+$: 559.1006; LC-MS: purity (UV)=96%, tR=24.92 min.

## 5-(2′-Fluorobiphenyl-2-yl)-1,3-dihydro-2*D*-1,4-benzodiazepin-2-one (6a)

The same method as for the synthesis of **4b** was used but acetic acid-$d_4$ (4 mL) was used instead of acetic acid as the solvent. The final product was obtained as a white powder; yield: 0.09 g (47%). $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta$=8.93 (s, 1H), 7.76–7.69 (m, 1H), 7.55–7.47 (m, 2H), 7.36–7.29 (m, 1H), 7.18 (pt, $J$=7.7 Hz, 1H), 7.05–6.83 (m, 5H), 6.72 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$=172.3, 171.0, 158.8 ($^{1}J_{C,F}$=246.8 Hz), 140.2, 137.3, 135.7, 131.4 (d, $^{3}J_{F,C}$=3.9 Hz), 131.2, 130.8, 130.0, 129.8, 129.5, 129.1 (d, $^{3}J_{F,C}$=7.9 Hz), 128.6, 128.1 (d, $^{2}J_{F,C}$=15.4 Hz), 127.9, 123.3 (d, $^{4}J_{F,C}$=3.6 Hz), 123.2, 120.2, 114.9 (d, $^{2}J_{F,C}$=22.2 Hz), 56.0 (m); $^{2}$H NMR (61 MHz, $CH_3CO_2H$): $\delta$=4.27 (s, 2H); HR-MS-ESI: $m/z$=333.1362, calculated for $C_{21}H_{13}D_2FN_2O$ [+H]$^+$: 333.1210; LC-MS: purity (UV)=97%, tR=11.06 min.

## 5-Biphenyl-2-yl-1,3-dihydro-2*D*-1,4-benzodiazepin-2-one (6b)

The same method as **1b** was used and the product was collected in quantitative yield. $^{1}$H NMR (500 MHz, DMSO-$d_6$): $\delta$=10.31 (s, 1H), 7.58–7.52 (m, 2H), 7.48 (d, $J$=7.4 Hz, 1H), 7.33 (d, $J$=7.4 Hz, 1H), 7.15 (pt, $J$=7.4 Hz, 1H), 7.10–7.03 (m, 3H), 6.91 (d, $J$=7.1 Hz, 2H), 6.81–6.75 (m, 2H), 6.70 (d, $J$=7.9 Hz, 1H); $^{13}$C NMR (126 MHz DMSO-$d_6$): $\delta$=173.2, 169.6, 141.5, 140.5, 139.8, 139.2, 131.3, 130.9, 130.2, 130.1, 129.4, 128.6 (2C), 128.3, 128.0 (2C), 127.6, 127.1, 122.6, 120.7, 57.0; $^{2}$H NMR (61 MHz, $CH_3CO_2H$): $\delta$=4.44 (2H); HR-MS-ESI: $m/z$=315.1453, calculated for $C_{21}H_{14}D_2N_2O$ [+H]$^+$: 315.1445.

## 5-(3′-Trifluorobiphenyl-2-yl)-1,3-dihydro-2*D*-1,4-benzodiazepin-2-one (6c)

The same method as **1b** was used and the product was collected in quantitative yield. $^{1}$H NMR (500 MHz, DMSO-$d_6$): $\delta$=10.20 (s, 1H), 7.61–7.51 (m, 3H), 7.43–7.28 (m, 3H), 7.19–7.10 (m, 3H), 6.80 (dd, $J$=8.4, 5.1 Hz, 2H), 6.72 (d, $J$=7.9 Hz, 1H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): $\delta$=171.7, 169.8, 141.6, 140.1, 139.9, 139.2 (2C), 132.6, 131.5, 130.9, 130.2, 129.6, 129.1 (q, $^{2}J_{F,C}$=31.7 Hz), 129.0, 128.4, 127.9, 124.9 (q, $^{3}J_{F,C}$=3.7 Hz), 124.3 (q, $^{1}J_{F,C}$=273.2 Hz), 123.8 (q, $^{3}J_{F,C}$=3.8 Hz), 122.6, 120.5, 56.5 ($CD_2$); $^{2}$H NMR (61 MHz, $CH_3CO_2H$): $\delta$=4.40 (2H); HR-MS-ESI: $m/z$=315.1453, calculated for $C_{22}H_{13}D_2F_3N_2O$ [+H]$^+$: 315.1445.

## 7-Chloro-1-methyl-5-(2′-fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (7a)

7-Chloro-5-(2′-fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one **5c** (0.035 g, 0.096 mmol) was dissolved in MeOH/THF (1 mL). Potassium carbonate (0.079 g, 0.57 mmol), iodomethane (0.03 mL, 0.48 mmol) were added and the reaction mixture was stirred overnight at room temperature. Thereafter the reaction mixture was filtered over celite, washed through with dichloromethane and concentrated under reduced pressure. The final product was collected as a white powder; yield: 0.033 g (91%). $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta$=7.79–7.73 (m, 1H), 7.54 (dd, $J$=6.3, 3.1 Hz, 2H), 7.34–7.28 (m, 1H), 7.19 (dd, $J$=8.9, 2.5 Hz, 1H), 7.12–7.05 (m, 1H), 6.96–6.88 (m, 3H), 6.83 (d, $J$=

8.9 Hz, 1H), 6.80–6.73 (m, 1H), 4.79 (d, $J=10.9$ Hz, 1H), 3.66 (d, $J=10.9$ Hz, 1H), 3.11 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta=170.3$, 169.3, 158.9 (d, $^1J_{F,C}=247.7$ Hz), 141.3, 138.9, 135.6, 131.4, 131.3, 131.0 (d, $^3J_{F,C}=8.0$ Hz), 130.8, 130.4, 129.9, 128.9, 128.8 (d, $^3J_{F,C}=8.0$ Hz), 128.7, 128.5 (d, $^2J_{F,C}=15.9$ Hz), 128.3, 123.4 (d, $^4J_{F,C}=3.6$ Hz), 121.4, 115.1 (d, $^2J_{F,C}=22.2$ Hz), 56.7, 35.0; HR-MS-ESI: $m/z=379.1012$, calculated for $C_{22}H_{16}ClFN_2O$ $[+H]^+$: 379.1008; LC-MS: purity (UV) = 98%, tR = 18.09 min.

### 7-Chloro-1-prop-2-yn-1-yl-5-biphenyl-2-yl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (7b)

7-Chloro-5-biphenyl-2-yl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (0.025 g, 0.072 mmol) was dissolved in MeOH/THF (1 mL). Potassium carbonate (0.060 g, 0.43 mmol), propargyl bromide (0.027 mL, 0.30 mmol) were added and the reaction mixture was stirred overnight at room temperature. Thereafter the reaction mixture was filtered over celite, washed through with dichloromethane and concentrated under reduced pressure. The final product was collected as a white powder; yield: 0.024 g (88%). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta=7.64$ (d, $J=7.6$ Hz, 1H), 7.59 (pt, $J=7.6$ Hz, 1H), 7.53 (pt, $J=7.6$ Hz, 1H), 7.41 (dd, $J=8.9$, 2.3 Hz, 1H), 7.34–7.27 (m, 2H), 7.19–7.12 (m, 3H), 6.86 (d, $J=7.0$ Hz, 2H), 6.67 (d, $J=2.5$ Hz, 1H), 4.81 (d, $J=17.5$ Hz, 1H), 4.58 (d, $J=10.9$ Hz, 1H), 3.74 (d, $J=10.9$ Hz, 1H), 3.43 (d, $J=17.5$ Hz, 1H), 3.37 (s, 1H); $^{13}$C NMR (126 MHz, DMSO-$d_6$): $\delta=170.8$, 168.1, 141.7, 140.9, 140.7, 138.2, 131.6, 131.3, 130.1, 130.7, 130.4, 128.6 (2C), 128.4 (2C), 128.3, 128.1, 128.0, 127.3, 121.8, 80.2, 75.2, 56.7, 38.0; HR-MS-ESI: $m/z=385.1108$, calculated for $C_{24}H_{17}ClN_2O$ $[+H]^+$: 385.1102; LC-MS: purity (UV) = 96%, tR = 20.90 min.

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